Efficacy and Safety of Gentamicin by Interval and Intravenous Dosage Adjustment based on the Gestational Age in Thai Neonates†

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Objective: *To determine the pharmacological efficacy and safety of the gentamicin regimen that adjusts intravenous dose and interval based on the gestational age (GA) in Thai neonates.*
Material and Method: *Neonates aged ≤ 7 days, who had received gentamicin for clinically suspected or high risk of sepsis and had no contraindication to gentamicin usage were enrolled. They were stratified into four groups by GA as ≤ 29, 30-33, 34-37 and ≥ 38 weeks gestation. Gentamicin administration in each group was 5, 4.5, 4 and 4 mg/kg/dose every 48, 36, 36 and 24 hours respectively according to* Neofax® *regimen. Peak serum gentamicin concentration (SGC), trough SGC and serum creatinine (Cr) were obtained.*
Results: *Forty-nine neonates were enrolled. Forty-four (89.7%) had peak SGC within the desirable range (5-12 mg/L). Three neonates had slightly high peak SGC. Their peak SGCs were 13.0, 12.21 and 12.20 mg/L. Two neonates had slightly low peak SGC. Their peak SGCs were 4.91 and 4.4 mg/L. All neonates had trough SGC below 2 mg/L. None had significant rising of serum Cr during the present study period.*
Conclusion: *This gentamicin regimen yielded good pharmacological efficacy and safety in Thai neonates, who were in the first week of life and had no renal function impairment.*

Keywords: *Efficacy, Safety, Gentamicin, Interval and intravenous administration*

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Gentamicin is one of the most commonly used antibiotics in neonates. It is inexpensive and highly effective against gram negative bacilli with a concentration dependent antibacterial action and post-antibiotic effect or the ability to suppress bacterial growth for a period of time after the drug level has fallen below the minimal inhibitory concentration (MIC) of the bacteria. The drawback to gentamicin usage is its narrow margin of safety. Adequate peak serum gentamicin concentration (SGC) and low trough SGC are required to achieve good bactericidal activity and reduce potential toxicity[1-3].

In neonates, as in adult and pediatric patients, evidence suggests that the use of large-dose, extended-interval gentamicin regimens are more likely to achieve optimum peak and trough concentration when compared to the traditional multiple daily dose regimens[3-7]. In addition, the adjustment of dose and dosage interval according to gestational age (GA) and birth weight is found to be suitable for premature infants[3,7-11]. Based on these rationales, several neonatal gentamicin dosing regimens have been proposed[3,7-15]. However, there is a wide variety among these protocols. The reason might be due to the fact that most of these protocols were derived from pharmacokinetic data of different demographic and clinical characteristic patient groups. When used in other racial populations, the result might not be the same. Caution has been expressed against generalized application of the developed protocols. To obtain optimal therapeutic effect and minimal side effects, drug level monitoring is usually advised[1,5,13,16].

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In most hospitals in Thailand, therapeutic drug monitoring cannot be done routinely, due to the limitation of laboratory capacity and budget. Since there is no uniformity in the recommended guidelines, clinicians have to decide which one would fit best to their institutes. For the Thai neonates, there have been a few studies about the use of a once daily dose gentamicin regimen. Prospective studies in term and near term neonates (≥ 34 weeks gestation) showed conflicting results. Chotigeat, et al found that when a dose of 4-5 mg/L once daily was used, none of the neonates had inappropriate trough SGC (> 2 mg/L)[17]. In contrast, Kosararaksa, et al found too high trough SGC in 22% of the studied group that received 5 mg/kg/day of gentamicin while subsequent study by Kiatchoosakun, et al showed that a once daily dose of 4 mg/kg gentamicin produced too high trough SGC in 6.67%[18,19]. Furthermore, there is no published clinical data concerning the use of extended interval dosing in Thai premature neonates.

In Chiang Mai University hospital, the gentamicin dosing regimen proposed by Young and Mangum, which was published in *Neofax*®, a widely used neonatal drug manual, was routinely applied. This regimen adjusts dose and dosing interval according to GA and postnatal age[14]. To validate the likelihood of the *Neofax*® regimen to attain the desirable SCG in the presented patients, the authors prospectively studied the use of this regimen in both term and preterm neonates. The results were aimed to provide guidance for the potential safety and efficacy of using this regimen in our neonatal population, while routine therapeutic drug monitoring was not available.

Objective

To determine the pharmacological efficacy and safety of the gentamicin dosing regimen that adjusts dose and dosing interval based on the GA of Thai neonates.

Material and Method

The present study was conducted at the Neonatal Unit, Chiang Mai University Hospital, Chiang Mai from October 2003 to February 2004. The present study protocol was approved by the Research Ethic Committee of the Faculty of Medicine, Chiang Mai University and informed consent was obtained from the parents.

The inclusion criteria consisted of neonates aged ≤ 7 days, who had received gentamicin as an empirical treatment for clinically suspected or high risk of sepsis. The exclusion criteria comprised neonates who had an elevated serum creatinine (Cr) level, were predisposed to abnormal kidney function, had contraindication to the use of gentamicin or had developed adverse reaction from gentamicin. The course and duration of therapy were determined by the attending physicians.

The neonates were stratified into four groups according to their GA. The dose and interval of gentamicin administration were according to *Neofax*® regimen[14] as follows:

GA ≤ 29 weeks 5 mg/kg/dose every 48 hours.
GA 30-33 weeks 4.5 mg/kg/dose every 36 hours.
GA 34-37 weeks 4 mg/kg/dose every 36 hours.
GA ≥ 38 weeks 4 mg/kg/dose every 24 hours.

Gentamicin doses were diluted with 3 milliliters of 5% dextrose in water, intravenous infused over 30 minutes with a syringe pump, followed by 1.5 milliliters normal saline solution flush.

One milliliter of blood was obtained 30 minutes after complete infusion of the first, third and sixth dose administration to determine the peak SGC and serum Cr level. The trough SGC was obtained within 30 minutes before the third and sixth dose. Blood samples were allowed to clot at room temperature, centrifuged for 5 minutes at 1,500 rpm to separate the serum, and kept at -20°C until assayed. The SGC was analyzed by the fluorescent polarization immunoassay

Table 1. Demographic data

	Group I GA ≤ 29 weeks	Group II GA 30-33 weeks	Group III GA 34-37 weeks	Group IV GA ≥ 38 weeks
n	10	10	14	15
Male / Female	3/7	6/4	8/6	9/6
GA, weeks (mean ± SD)	27.0 ± 2.1	31.3 ± 1.2	35.6 ± 1.3	39.6 ± 1.4
Birth weigh, gram (mean ± SD)	767.0 ± 287.0	1,351.0 ± 258.0	2,392.0 ± 371.0	3,102.0 ± 491.0
Age, day (mean ± SD)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.1 ± 0.4
Duration of therapy, day (mean ± SD)	5.1 ± 2.3	5.4 ± 2.5	7.1 ± 2.7	6.0 ± 1.7

(FPIA) technique, using the Abbot TDX clinical analyzer (Abbot Laboratory, North Chicago, IL, USA).

Statistical analysis for the differences among the peak SGC (mean, standard deviation: SD) obtained after the first, third and sixth dose was determined by analysis of variance (ANOVA). The difference between the peak SGC obtained after the first and third dose and the trough SGC obtained before the third and fifth dose was determined by the student *t* test. A p-value of less than 0.05 was considered significant.

Results

Forty-nine neonates were enrolled. The number of neonates in group I, II, III and IV were 10, 10, 14 and 15, respectively. Baseline characteristics are shown in Table1. Most of the neonates were enrolled on the first day of life except two, who were 2 days old. The indications for gentamicin therapy were respiratory distress, prolonged rupture of the membrane and suspected sepsis. The duration of treatment ranged between 1-11 days. None of the studied neonates had positive blood culture nor died due to infection during the evaluation period. The serum Cr levels of all neonates when receiving the first dose were within the normal limit for age. For neonates who received the third and sixth dose, none of the Cr levels that obtained at the same time with peak SGC, increased to abnormal range. There was no adverse drug reaction recognized.

Fourteen neonates received ≥ 6 doses of gentamicin, 27 received 3-5 doses and nine received less than three doses. One hundred and three peak SGCs and 54 trough SGCs were obtained. Three peak SGCs were excluded from the analysis due to error in sampling time and dosage. In total, 100 peak SGCs and 54 trough SGCs were analyzed.

The peak and trough SGC in each group are presented in Table 2. There was no statistical difference between the peak SGC obtained after the first, third and sixth dose in all groups ($p > 0.05$). The trough SGC before the third and sixth doses was obtained only from neonates in group III and IV because none of those in group I and II received gentamicin more than five doses. In group III neonates, trough SGC before the sixth dose was significantly lower than that before the third dose ($p = 0.005$), but in group IV, there was no statistical difference ($p = 0.140$).

Table 3 displays the number and percentage of neonates with various peaks and trough SGC. Out of 49 neonates, 44 (89.7%) had a peak SGC within the desirable range (5-12 mg/L) and none had a trough

Table 2. Peak and trough SGC

	Group I GA ≤ 29 week		Group II GA 30-33 week		Group III GA 34-37 week		Group IV GA ≥ 38 week	
	Mean ± SD (n)	p-value	Mean ± SD (n)	p-value	Mean ± SD (n)	p-value	Mean ± SD (n)	p-value
Peak SGC								
After first dose	8.80±1.80 (10)	0.166[a]	7.86±1.47 (10)	0.117[a]	6.91±1.18 (13)	0.356[b]	7.44±1.43 (14)	0.077[b]
After third dose	10.45±2.09 (6)		9.32±1.69 (7)		6.87±1.24 (11)		8.15±1.62 (15)	
After sixth dose	NA*		NA*		7.74±0.90 (5)		6.90±1.34 (9)	
Trough SGC								
Before third dose	0.99±0.41 (7)	-	0.66±0.28 (7)	-	0.51±0.29 (10)	0.005[a]	0.90±0.54 (15)	0.140[a]
Before sixth dose	NA*		NA*		0.18±0.13 (5)		0.63±0.36 (9)	

* NA = not available
a: p-value by student t-test
b: p-value by ANOVA

SGC of > 2 mg/L. A trough SGC of < 1 mg/L, < 0.5mg/L and 0.5-1mg/L was found in 70.7%, 36.6% and 34.1% respectively.

Five neonates had SGC out of the target range. Three neonates, who had a peak SGC of > 12 mg/L, were at 25, 29 and 30 weeks gestation, and their peak SGC was 13.0, 12.21 and 12.20 mg/L, respectively. Two neonates had a peak SGC of < 5 mg/L. They were at 35 and 39 weeks gestation, and their peak SGC was 4.91 and 4.4 mg/L respectively. The details are shown in Table 4.

Discussion

In clinical practice, the efficacy of antibiotic therapy in neonates is difficult to determine. Most of the prescribed antibiotics are for suspected or high risk of infection rather than culture proven sepsis. Moreover, the incidence of culture positive sepsis in neonates is usually lower than it should actually be, due to the limited amount of blood obtained for culture and prenatal antibiotic treatment in mothers[20,21]. Therefore, pharmacokinetic parameters are usually used to demonstrate the efficacy[20]. For aminoglycosides, the efficacy is determined by high peak serum concentration. Studies in adult patients have shown that a higher peak SGC correlates with better clinical outcome in severe infection[22,23]. Currently, more authors prefer a peak SGC of at least 5 mg/L to the traditional level of 4 mg/L. The commonly accepted peak SGC is 5-12 mg/L[3,4,7,10,14].

In the present study, 89.7% of studied neonates had a peak SGC in the desirable range, and 95.9% had peak SGC more than 5 mg/L. In the three neonates who had a high peak SGC, their serum levels were slightly higher than 12 mg/L. Such levels are not considered to be harmful, since the toxicity did not associate with transient elevation of the SGC[1,3,24]. Only two neonates had sub-therapeutic peak SGC, but their peak SGC was still more than the traditional target of 4 mg/L. Therefore, the regimen we implemented yielded good pharmacological efficacy.

Recently, Murphy published a study that evaluated the ability of six gentamicin dosing regimens to achieve the desired SGC by using pooled retrospective pharmacokinetic data from three previously published articles. In that study, the capacity of the

Table 3. Number and percentage of neonates with desired peak and trough SGC

	Group I GA ≤ 29 weeks	Group II GA 30-33 weeks	Group III GA 34-37 weeks	Group IV GA ≥ 38 weeks	Total
Peak SGC 5-12 mg/L, n (%)	8/10 (80.0)	9/10 (90.0)	13/14 (92.9)	14/15 (93.3)	44/49 (89.8)
Peak SGC < 5 mg/L, n (%)	0/0 (0)	0/10 (0)	1/14 (7.1)	1/15 (6.7)	3/49 (4.1)
Peak SGC > 12 mg/L, n (%)	2/10 (20.0)	1/10 (10.0)	0/14 (0)	0/15 (0)	3/49 (6.1)
Trough SGC < 2 mg/L, n (%)	7/7 (100)	7/7 (100)	12/12 (100)	15/15 (10)	41/41 (100)
Trough SGC < 1 mg/L, n (%)	3/7 (42.9)	6/7 (85.7)	11/12 (91.7)	9/15 (60)	29/41 (70.7)
Trough SGC < 0.5mg/L, n (%)	1/7 (14.3)	2/7 (28.6)	6/12 (50.0)	6/15 (40.0)	15/41 (36.6)
trough SGC 0.5-1 mg/L, n (%)	2/7 (28.6)	4/7 (57.1)	4/12 (33.3)	4/15 (26.7)	14/41 (34.1)

Table 4. Characteristics of neonates with a peak SGC of > 12 mg/L or < 5 mg/L

GA (week)	Birth weight (gram)	Peak SGC (mg/L) after			Trough SGC (mg/L) before		Serum Cr (mg/dL) after		
		1st dose	3rd dose	6th dose	3rd dose	6th dose	1st dose	3rd dose	6th dose
29	1,080	12.21	11.97	NA	1.10	NA	1.10	1.00	NA
25	440	13.00	NA	NA	0.96	NA	0.80	NA	NA
30	1,280	8.83	12.20	NA	0.59	NA	0.80	0.80	NA
35	2,450	4.91	6.29	NA	0.12	0.05	1.00	0.20	NA
39	3,970	4.40	4.71	NA	0.33	NA	0.90	0.50	NA

* NA = not available

Neofax® regimen to obtain a peak SGC of < 5 mg/L and > 12.5 mg/L was 1.7% and 7.2%, respectively[25]. When compared to the present prospective study, the percentage of those who had SGC out of desirable range was similar.

The safety of gentamicin is determined by trough concentration. In adult studies, a trough SGC of higher than 2 mg/L and prolonged therapy for more than 10 days related to toxicity[1,3,24]. For the large-dose, extended-interval dosing regimens in neonates, the target trough SGC varied, due to concerns about the risk of exposing quite high SGC for a long duration and a break through of infection from SGC that is too low for several hours before the next dose. Thus, some authors preferred the trough SGC to be less than 1 mg/L and some considered the trough SGC lower than 0.5 mg/L to be suboptimal[9,16,20,25]. The *Neofax*® regimen recommends a trough SGC of 0.5-1 mg/L. Murphy's study indicated that the likelihood of six different protocols to achieve a trough level of 0.5-1 mg/L ranged from 26.9% to 68.3%[25]. In the present study, 34.1% of neonates obtained a trough SGC in this range.

However, the incidence of gentamicin nephrotoxicity and ototoxicity in neonates is not well established and seems to be considerably less than that in adults[3,20,26]. Moreover, there is not enough evidence to show that a trough SGC of 1-2 mg/L is associated with more toxicity in neonates. No study could demonstrate that too low a trough SGC leads to more treatment failure. Therefore, most authors still consider trough SGC of lower than 2 mg/L as a safe limit for neonates[4-6,10,11,13,15,17-19]. In the present study, the authors did not follow the serum Cr level after discontinuation of therapy or perform a hearing assessment to determine the clinical safety, but all of the neonates had trough SGC below the potential toxic level. In addition, none had significant rising of serum Cr during the study period.

For protocols that use multiple daily doses of gentamicin, drug level monitoring should be done at a steady state or after 3-5 doses have been administered. In the large-dose, extended interval regimens, some authors suggested that the peak SGC could be measured after the first dose or second dose[14,15,27]. The present data support this opinion, since the peak SGC obtained after the first dose was not different from those obtained after the third and sixth doses. The authors did not measure the trough SGC of the first dose, so the authors could not decide whether it can be used to determine the trough SGC at a steady state. The trough SGC before the sixth dose were significantly lower than that before the third dose in 34-37 week gestation neonates, and slightly lower but not statistically significant in those who were ≥ 38 week gestation. This might reflect the postnatal maturation of their renal function.

Although the best way to assure efficacy and safety of neonatal gentamicin therapy is to customize the dose and dosing interval according to the pharmacokinetic of individual patients, there is a variety of suggestions for therapeutic drug monitoring. Some authors did not recommend doing this routinely[3,6,15]. Therapeutic drug monitoring requires more frequent blood tests and adjustment of dosage or interval, which lead to additional cost and potential for prescription or administration errors. In Thailand, drug level monitoring is not practical in every hospital. The present study has demonstrated good pharmacological efficacy and safety of the gentamicin regimen, which adjusted the dose and interval according to gestational age. The number of neonates studied might be too small to make a definite recommendation, but the authors believe that for neonates who are in the first week of life and have no renal function impairment, therapeutic drug monitoring is not required especially in those who received gentamicin for a short-term course. Further study in neonates who are older than 7 days or receiving a longer course of treatment is warranted.

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ประสิทธิภาพและความปลอดภัยของการใช้ยาเจนตาไมซินโดยปรับระยะห่างและขนาดของการบริหารยาเข้าเส้นเลือดดำตามอายุครรภ์ของทารกแรกเกิดไทย

วัชรี ตันติประภา, สุจิตรา จันทรคณา, สมพร โชตินฤมล, นพมาศ โรจนเสถียร

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพและความปลอดภัยของวิธีการใช้ยาเจนตาไมซิน โดยปรับขนาดยา และระยะห่างของการให้ยาตามอายุครรภ์ของทารกแรกเกิดไทย*

วัสดุและวิธีการ: *ศึกษาในทารกที่อายุ ≤ 7 วัน ซึ่งได้รับยาเจนตาไมซิน เพื่อรักษาภาวะติดเชื้อ และไม่มีข้อห้ามต่อการใช้ยานี้ แบ่งทารกเป็น 4 กลุ่ม ตามอายุครรภ์ ดังนี้ คือ ≤ 29, 30-34, 35-37 และ ≥ 38 สัปดาห์ โดยให้ยาในขนาด 5, 4.5, 4 และ 4 มิลลิกรัม/กิโลกรัม/ครั้ง ให้ยาทุก 48, 36, 36 และ 24 ชั่วโมงตามลำดับ แล้วทำการวัดระดับยาที่ระดับสูงสุดและต่ำสุด รวมทั้งค่า serum Cr*

ผลการศึกษา: *ทารกเข้ารับการศึกษาทั้งหมด 49 ราย พบว่า 44 ราย (89.7%) มีระดับยาสูงสุด ที่เหมาะสมคือ 5-12 มิลลิกรัม/ลิตร ทารก 3 ราย มีระดับยาสูงสุดสูงเกินเล็กน้อย คือ 13.0, 12.21 และ12.20 มิลลิกรัม/ลิตร และทารก 2 รายมีระดับสูงสุด ต่ำกว่าระดับสูงสุดที่เหมาะสมเล็กน้อย คือ 4.4 และ 4.91 มิลลิกรัม/ลิตร ส่วนระดับต่ำสุดในทารกทุกรายอยู่ในระดับเหมาะสมคือต่ำกว่า 2 มิลลิกรัม/ลิตร และไม่พบทารกที่มีค่า serum Cr เพิ่มผิดปกติในระหว่างการศึกษา*

สรุป: *การให้ยาเจนตาไมซิน มีประสิทธิภาพและความปลอดภัยดี ในทารกไทยที่มีอายุไม่เกิน 7 วัน ซึ่งไม่มีความผิดปกติในการทำงานของไต*